REMARKS

Claims 17-32 were pending in the instant application. Claims 24 and 32 have been withdrawn from consideration by the Examiner. Claims 17-23 and 25-32 have been rejected. Further, claims 17-21, 23, 25-29 and 32 have been objected to. Claims 17-32 have been canceled and the subject matter represented in new claims 33 through 44. Support for these amendments is provided in the original claims as well as teachings throughout the specification, for example, at page 15, lines 2-23, page 18, line 16 through page 19, line 5 and page 36, line 15 through page 39, line 6. No new matter is added by these amendments. Reconsideration in light of these amendments and the following remarks is respectfully requested.

I. Finality of Restriction Requirement

The Examiner has withdrawn the Restriction Requirement mailed July 14, 2006 with respect to Groups I and II. With regard to the election of species, however, the Examiner has maintained the requirement and withdrawn claims 24 and 32. While claims 24 and 32 have been canceled by this amendment, it is respectfully requested that subject matter of these claims (new presented in new claims 39 and 44) be rejoined

upon allowance of the generic claims in accordance with MPEP § 809.01 and 37 C.F.R. § 1.146.

II. Objection to Specification

The specification has been objected to. Specifically, the Examiner suggests that the specification must be amended to include Sequence Identifiers adjacent to sequences disclosed at page 7, line 1 of the specification. Further, the Examiner suggests that the trademarks TRITON and TWEEN must be capitalized and accompanied by the generic terminology.

Accordingly, in an earnest effort to advance the prosecution of this case, Applicants are submitting herewith an amended paper copy and CRF copy of a sequence listing inclusive of the peptides disclosed at page 7, line 1 as SEQ ID NO: 11 and SEQ ID NO:12. Further, Applicants have amended the specification to include the appropriate sequence identifiers adjacent to these peptides as well as peptides described at page 15.

A statement in accordance with 37 C.F.R. 1.821-1.825 is also being submitted herewith.

Further, Applicants have amended the specification to capitalize the trademarks TRITON and TWEEN and to include generic terminology with the trademarks.

Withdrawal of these objections is therefore respectfully requested.

III. Objection to Claims 17-21, 23, 25-29 and 32

Claims 17-21, 23, 25-29 and 32 have been objected to for multiple informalities.

Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have canceled claims 17-32 and represented the subject matter of these claims in new claims 33-44. In new claims 33-44 the first instance of any abbreviation is accompanied by the full term; any prior steps designated a, b, c, etc. are referred to correctly via letter, not by a number or the phrase "the above step"; standard Markush language is used; the phrases/words "specific binding reaction" and "binding reaction", as well as "any body fluid" and "ligands" versus "ligand" are no longer used; an article is placed before the term "matrix" and "antibody"; kits claims include the word "diagnosing" and present the components in a clear manner; and the phrase coloring substrate has been replaced with "colorimetric substrate" in the claims and specification as suggested by the Examiner.

Thus, new claims 33 through 44 are believed to overcome all pending objections to the claims and withdrawal is respectfully requested.

IV. Rejection of Claims 1-23 and 25-31 under 35 U.S.C. 112, first paragraph - Written Description

Claims 1-23 and 25-31 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner suggests that the specification does not provide a written description to support evidence of possession of the genus of fragments or derivatives of βig-h3 proteins or the genus of ligands thereto.

It is respectfully pointed out that Applicants have canceled claims 1-23 and 25-31 and represented the subject matter in new claims 33-44. New claims 33-44 are no longer drawn to fragments or derivatives of βig-h3 proteins or non-antibody ligands thereto.

Withdrawal of this rejection under 35 U.S.C. 112, first paragraph, for lack of written description is therefore respectfully requested.

V. Rejection of Claims 17-23 and 25-31 under 35 U.S.C. 112, first paragraph - Lack of Enablement

Claims 17-23 and 25-31 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The Examiner suggests that the specification fails to teach the skilled artisan how to make and use the claimed invention for diagnosing all renal disease, all hepatic diseases, all cardiovascular diseases, as well as rheumatoid arthritis by measurement of βig-h3 protein in all types of samples.

Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have canceled claims 17-23 and 25-31 and represented the subject matter in new claims 33 through 44 drawn to methods and kits for diagnosing damage to kidneys at an early stage in a subject via detection of βig-h3 protein in urine samples. These claims are supported by the original claims as well as teachings in the specification in Example 4, particularly part 4-1, which provides evidence that measuring the amount of βig-h3 in patients' urine is a highly sensitive and important diagnostic method that can reflect the damage of kidneys in the early stage, and 4-2, which provides results from a diabetic animal model confirming that the βig-h3

concentration in urine can reflect the renal damage in the early stage.

Applicants respectfully disagree with the Examiner's suggestion that results in Table 1 showing an increase in βig-h3 levels in diabetic patients without renal disease are indicative of a "false positive reading". Those skilled in the art recognize that diabetic renal disease generally develops slowly and only shows clinical symptoms after a very long-term silent period. While diabetes mellitus is the most common cause of adult kidney failure world wide, diabetic renal disease is typically not diagnosed in patients with chronic diabetes until 15 or more years after onset of diabetes mellitus. This is because the first stage of diabetic renal disease defined as "latent diabetic glomerulophthy", which can last for up to ten years, can not be diagnosed by conventional detection methods. Thus, those skilled in the art would not view data in Table 1 for diabetic patients without clinical symptoms of renal disease as a false positive but rather recognize that the present invention provides for an unsolved need not met by conventional detection methods, namely detection of early stage kidney damage as claimed.

Further, the utility of measuring βig-h3 levels in urine as an indicator of damage to the kidney at an early

stage was confirmed in a diabetic animal model (See Example 4-2). As shown therein, while blood urea and creatinine were normal and kidney tissues seemed normal in the diabetic animal model at day 5, the βig-h3 concentration was increased on average by 4-fold 5 days after inducing diabetes (see FIG. 13 and 14). This measurable increase of βig-h3 levels in urine on the fifth day is indicative of early damage to the kidneys, which could not be detected by the traditional test methods.

Thus, Applicants believe the instant specification provides adequate guidance for one of skill in the art to make and use the invention as now claimed, thereby meeting the enablement requirements of 35 U.S.C. 112, first paragraph.

Withdrawal of this rejection under 35 U.S.C. 112, first paragraph is therefore respectfully requested.

VI. Rejection of Claims 1-23 and 25-31 under 35 U.S.C. 112, second paragraph

Claims 1-23 and 25-31 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have canceled claims 17-32 and represented the subject matter in new claims 33 through 44. New claims 33 through 44 include a step about determining if damage to the kidneys is present in the subject, based on the measured amount of βig-h3 protein of the urine sample being increased as compared to a normal urine sample. New claims 33 through 44 no longer recite a step of preparing recombinant proteins. The new claims also no longer refer to the method of the preamble or recite fragment or derivatives or ligands. Further, it is believed that sufficient antecedent basis is provided for all elements in the new claims. In addition, it is believed that the new claims overcome any indefiniteness regarding the sample tested.

Further with respect to the Examiner's suggestion that the recitation of the 4th fas-1 domain is unclear, Applicants have amended the specification at page 15 to include the sequence identifier of SEQ ID NO:6 adjacent to the description of this domain as well as the sequence identifiers of SEQ ID NO;7, 8, 9 and 10, adjacent to the exemplary encoded recombinant peptides comprising one or more of these domains. The new claims also include these limitations. As these sequences were included in the

original sequence listing, no new matter is added by this amendment. Applicants believe these amendments clarify what is meant by fas-1 domain in accordance with the present invention.

Withdrawal of these rejections under 35 U.S.C. 112, second paragraph, is therefore respectfully requested.

VII. Rejection of Claims 26-27 and 29-31 under 35 U.S.C. 102(a) or 102(e)

Claims 26-27 and 29-31 have been rejected under 35 U.S.C. 102(a) or 102(e) as being anticipated by Kim et al. (WO 01/87327 A1). The Examiner suggests that Kim et al. teach a kit comprising βig-h3 protein and ligands thereof (the integrin α3β1, contained in HCE cells).

Applicants respectfully traverse this rejection.

It is respectfully pointed out that claims 26-27 and 29-31 have been canceled. Subject matter of these claims is represented in new claims 33 through 44 drawn specifically to antibodies of βig-h3 or βig-h3 fas-1 domain. Since Kim et al. do not teach antibodies of βig-h3 or βig-h3 fas-1 domain, this reference cannot anticipate the instant claims.

Withdrawal of this rejection under 35 U.S.C. 102(a) or 102(e) is therefore respectfully requested.

VIII. Rejection of Claims 17-23, 25 and 26-31 under 35 U.S.C. 103(a)

Claims 26-31 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow & Lane (Antibodies:A Laboratory Manual (1988) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pages 558-559, 570-576, 586-589 and 591-593) in view of Gilbert et al. (Kidney International 1998 54:1052-1062) and Zuk et al. (U.S. Patent 4,208,479). The Examiner suggests that it would have been obvious to one of ordinary skill in the art to employ the competition assay format of Harlow & Lane, which employs a sample of the protein to be detected, in order to detect βig-h3 because Gilbert et al. teach that this protein is an index of TGF-β1 bioactivity in the kidney. The Examiner suggests that it would have been further obvious to package all of the reagents necessary for performing such an assay into a kit as taught by Zuk et al. for convenience.

Claims 17-23 and 25 have also been rejected under 35 U.S.C. 103 as being unpatentable over Harlow & Lane in view of Gilbert and Ratti et al. (U.S. Patent 5,659,167). The Examiner suggests that it would have been obvious to one skilled in the art to employ the method of detecting antigens of Harlow & Lane in order to detect βig-h3 since

Gilbert et al. teach that βig-h3 may be used as an index of TGF-β1 bioactivity in the kidney. With respect to the limitation that the protein is recombinant, the Examiner suggests that Ratti et al. teach a significant advantage of producing protein by recombinant DNA techniques rather than by isolating and purifying a protein from natural sources.

Applicants respectfully traverse these rejections.

As discussed above, claims 17 through 32 have been canceled. Subject matter from these claims is represented in new claims 33 through 44 drawn to method and kits for diagnosing damage to kidneys at an early stage via detection of βig-h3 in a urine sample from the subject.

In contrast, Gilbert et al, the only reference cited by the Examiner which actually relates to βig-h3, teaches that expression of βig-h3 is increased in the kidneys of rats with experimentally-induced diabetes. However, nowhere does this reference or Harlow & Lane, Zuk or Ratti et al. teach or suggest detection of this protein in urine as an indicator of early kidney damage.

Thus, since the cited combinations of references do not teach or suggest all the limitations of the instant claims, they cannot establish a prima facie case of obviousness with respect to the instant claimed invention. See MPEP 2143.

Withdrawal of these rejections under 35 U.S.C. 103(a) is therefore respectfully requested.

IX. Conclusion

Applicants believe that this submission overcomes all pending rejections in this case and comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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